



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵: C07H 1/00	A1	(11) International Publication Number: WO 94/21653 (43) International Publication Date: 29 September 1994 (29.09.94)
(21) International Application Number: PCT/US94/02366 (22) International Filing Date: 4 March 1994 (04.03.94) (30) Priority Data: 08/035,421 22 March 1993 (22.03.93) US (71) Applicant: GENERAL ELECTRIC COMPANY [US/US]; 1 River Road, Schenectady, NY 12345 (US). (72) Inventors: JOHNSON, Bruce, Fletcher; 36 Irving Road, Scotia, NY 12302 (US). KISELEV, Maxim, Yurievich; Apartment 4, 1815 S. West Avenue, Waukesha, WI 53186 (US). ULIN, Johan; Krougatan 37, S-752 38 Uppsala (SE). (74) Agents: CHASKIN, Jay, L. et al.; General Electric Company, 3135 Easton Turnpike, Fairfield, CT 06431-0001 (US).		(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: METHOD FOR MAKING 2-FLUORO-2-DEOXYGLUCOSE (57) Abstract A method is provided for preparing [¹⁸ F]2-fluoro-2-deoxyglucose with an anion exchange resin by effecting an exchange reaction between an aqueous solution of [¹⁸ F]fluoride containing an alkali metal carbonate or bicarbonate, such as sodium bicarbonate, and an anion, such as bicarbonate or carbonate, on the anion exchange resin followed by the displacement reaction with 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose to form the resulting 2-fluoro-2-deoxyglucose tetraacetate. Improved yields of the [¹⁸ F]2-fluoro-2-deoxyglucose are obtained when the alkali bicarbonate or carbonate is used in the target water.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

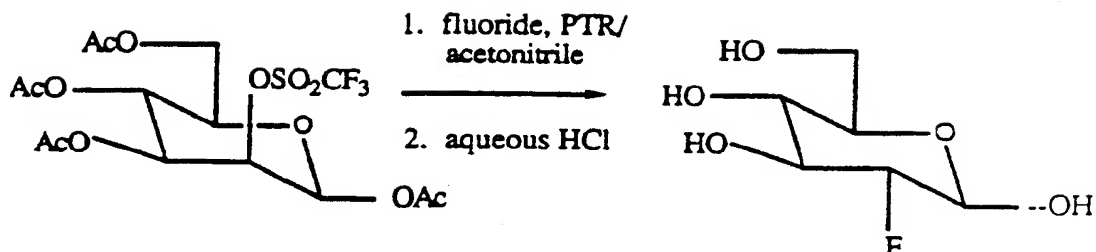
AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

METHOD FOR MAKING 2-FLUORO-2-
DEOXYGLUCOSE

Background of the Invention

The present invention relates to a method
5 for making 2-fluoro-2-deoxy-D-glucose or [^{18}F]2FDG ,
utilizing an anion exchange resin. More particularly,
the present invention relates to the use of an anion
exchange resin to more effectively trap [^{18}F]fluoride
ion, involving the treatment of the anion exchange
10 resin having an anion, such as a carbonate or
bicarbonate anion, with an aqueous solution of
[^{18}F]fluoride ion target water and an alkali metal
carbonate or bicarbonate salt, such as sodium
bicarbonate.

15 Prior to the present invention, various
procedures were used for making [^{18}F]2FDG, which is
used as a radiopharmaceutical for Positron Emission
Tomography (PET). Considerable effort has been
expended in the development and refinement of such
20 procedures. Because [^{18}F]fluoride ion has a low decay
energy, (0.64 MEV), it allows the highest inherent
resolution during PET measurements and has a
relatively convenient half life of 109.7 min. The
following equation illustrates the preferred procedure
25 for making [^{18}F]2FDG starting tiwh a solution of
1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -
D-mannopyranose or "triflate":



5 where Ac is acetate, and "PTR" means phase-transfer reagent.

One method of synthesizing [^{18}F]2FDG by the above procedure is shown by Hamacher et al., Journal of Nuclear Medicine, 27:235-238, (1986). Hamacher et al. employ an aminopolyether [Kryptofix 222 or K222]-potassium carbonate complex as a phase-transfer catalyst for [^{18}F]fluoride. An additional procedure for making [^{18}F]2FDG is shown by Brodack et al., Applied Radiation and Isotope, Volume 39, No. 7, pages 699-703 (1988) involving the employment of a tetrabutylammonium hydroxide as a phase-transfer catalyst in place of the aminopolyether potassium complex of Hamacher et al. Although Brodack et al. disclose that the triflate reacts with [^{18}F]fluoride ion using the tetrabutylammonium counter ion, a yield of 12-17% is reported which is significantly below the level considered acceptable for commercial robotic production of [^{18}F]2FDG.

The above procedures utilizing a phase-transfer reagent for [^{18}F]2FDG synthesis have an inherent disadvantage particularly if Kryptofix 222 is

used as the phase-transfer catalyst. Kryptofix is toxic and minor traces of the phase-transfer catalyst are often difficult to remove from the final patient dose. Elaborate methods have to be used therefore to eliminate any traces of the phase-transfer catalyst before it is used. The application of automation using such PTR is therefore rendered more difficult.

An improvement in the use of a phase-transfer catalyst for making [^{18}F]2FDG is shown by Johnson et al., U.S. Patent 5,169,942 which utilizes a less toxic PTR, such as a tetraalkylammonium bicarbonate. However, it has been found desirable to minimize any traces of the PTR from the final dose before intravenous use which complicates the implementation of this procedure.

As shown by S. A. Toorongian et al., cited below, alternative methods for making [^{18}F]2FDG are also known which utilize an anion exchange resin to trap the [^{18}F]fluoride ion. However, the yields of [^{18}F]2FDG made by the anion exchange resin procedure have been found to be significantly less than methods employing a PTR. It would be desirable therefore to provide a procedure for improving the yield of [^{18}F]2FDG by using an anion exchange resin to more effectively trap the [^{18}F]fluoride ion and improve the yields of [^{18}F]2FDG.

Summary of the Invention

The present invention is based on the discovery that improved yields of [^{18}F]2FDG can be obtained with an anion exchange resin having a carbonate or bicarbonate anion. It has been found that if prior to direct contact between the [^{18}F]fluoride ion containing target water and the

anion exchange resin, the [^{18}F]fluoride ion target water is mixed with an alkali metal carbonate or bicarbonate salt in proportions as set forth below, an enhancement in [^{18}F]2FDG yields can be obtained.

5

Statement of the Invention

There is provided by the present invention, a method for making [^{18}F]2-fluoro-2-deoxy-D-glucose comprising,

comprising a silanol-free organosilicon resin powder made in accordance with claim 1, a vinyl substituted methylpolysiloxane fluid, a silicon hydride siloxane fluid, an inhibitor and an effective amount of a platinum catalyst. (2) effecting the displacement of the [^{18}F]fluoride ion on the anion exchange resin of (1) with the trifluoromethanesulfonyl ester leaving group of an organic solvent solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose,

(3) treating with an aqueous hydrogen halide solution, the residue of the effluent of (2), after it has been collected from the anion exchange resin and stripped of organic solvent to effect the hydrolysis of the resulting tetraacetyl 2-fluoro-2-deoxyglucose, and

(4) recovering the resulting [^{18}F]2-fluoro-2-deoxyglucose from (3).

Among the ion exchange resins which can be employed are for example, polystyrene resin functionalized with piperidinopyridinium groups which serve to trap the [^{18}F]fluoride ion and act as a phase-transfer reagent without contaminating the mixture which is injected into the patient. The preferred anion exchange resin is the "Mulholland"

anion exchange resin which preferably has a displaceable carbonate or bicarbonate anion ionically bound to the pyridinium group.

During the initial exchange reaction
5 between the anion exchange resin and the [^{18}F]fluoride ion, the [^{18}F]fluoride ion is introduced as an aqueous solution with an alkali metal carbonate or bicarbonate salt. Although sodium bicarbonate is preferred other
10 alkali metal bicarbonates or carbonates can be used, such as potassium bicarbonate and sodium carbonate. The [^{18}F]fluoride ion is preferably added to an aqueous solution of the alkali metal bicarbonate within the aforescribed concentration ranges as set forth in the Statement of The Invention.

15 After passage of the aqueous solution of [^{18}F]fluoride ion and alkali metal bicarbonate or carbonate through the anion exchange resin to effect exchange and more effectively trap the [^{18}F]fluoride ion on the anion exchange resin, the anionic exchange
20 resin can be treated with an anhydrous organic solvent such as acetonitrile to remove water. The anionic exchange resin can then be heated from 70°C to 90°C prior to passage of an organic solvent solution of the "triflate", 3,4,6-tetra-O-acetyl-2-O-
25 trifluoromethanesulfonyl- β -D-mannopyranose to effect exchange between the triflate leaving group and the [^{18}F]fluoride ion. The anionic exchange resin can then be rinsed with additional organic solvent.

The effluent from the anionic exchange
30 resin can be stripped of organic solvent under a stream of nitrogen or helium under reduced pressure. The residue can then be treated with an aqueous acid halide, such as an 2 N HCl solution and refluxed for a sufficient period of time, such as 10 to 20 minutes to
35 effect the hydrolysis of the [^{18}F]2FDG tetraacetate.

- 6 -

The resulting solution can then be passed through ion retardation resin, reverse phase silica gel and an alumina sep-pak into a collection vial. Radioactivity in the collection vial can be measured and the purity assessed by TLC.

In order that those skilled in the art will be better able to practice the present invention, the following example is given by way of illustration and not by way of limitation. All parts are by weight.

Example

There was added 0.5 to 1.5 μ mol of sodium bicarbonate and 10 to 500 μ l of deionized water to 1.0 to 1.5 ml of water which was obtained from a cyclotron target containing 0.5 to 10 mCi of [^{18}F]fluoride in a receiver vessel. The resulting solution was passed through a column having 10-20 mg of a 2% crosslinked anion exchange resin, specifically (Mulholland) anion exchange resin in the carbonate form, (shown by S.A.Toorongian et al; NuCl.Med.Biol.17:273-279 (1990)Int. J. Radiat. Appl. Instrum. Part B). One ml of dry acetonitrile was then passed through the resin to remove water. The anion exchange resin was then heated to 80 to 90°C and a solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose (triflate) in acetonitrile where the solution contained 30 mg of the (triflate) in 0.75 ml of acetonitrile, was pushed through the resin column to effect displacement. The column was then rinsed with 0.5 ml of acetonitrile. Effluent was collected in a plastic vessel and the acetonitrile was removed in a stream of nitrogen with heating under reduced pressure. The resulting residue was then treated with 2 ml of 2 N hydrochloric acid and refluxed for 15 minutes to effect hydrolysis of the [^{18}F]2FDG

SUBSTITUTE SHEET (RULE 26)

tetraacetate. The resulting solution was passed through an ion retardation resin (Biorad AG-11A8), reverse phase C18 silica gel (Supelco SPE), (Waters) and alumina sep pak (Waters) to a collection vial.

- 5 The radioactivity in the collection vial was measured and the purity assessed by TLC. The following results were obtained where the reported yields are not decay corrected, and n is the number of runs:

10

Table 1Yields of [¹⁸F]2FDG

15	0.5 μ mol NaHCO ₃ <u>in Target Water</u>	<u>Yield</u>	95% <u>confidence level</u>	<u>n</u>
	Yes	39.5%	4.4%	7
	No	35.7%	2.3%	21

20

The above procedure was repeated except that the yield of the [¹⁸F]2FDG tetraacetate was measured. There was used 0.3 μ mol of sodium bicarbonate solution in the target water and the column was heated at 80°C to 90°C. The following

25

results were obtained where the yields are corrected for decay:

Table 2Yields of [¹⁸F]2FDG Tetraacetate

5	0.3 μ mol NaHCO ₃	Column	Yield	95%	n
	<u>In Target Water</u>	<u>Temp (°)</u>		<u>confidence level</u>	
	Yes	90°C	69.6%	4.7%	12
	No	90°C	56.0%	11.7%	4
	Yes	80°C	69.4/1%	2.5%	5
10	No	80°C	53.3%	9.0%	6

As shown by the results in Tables 1 and 2, significantly improved yields of [¹⁸F]2FDG and the corresponding tetraacetate were obtained when NaHCO₃ was used in the target water in accordance with the practice of the present invention.

Although the above example is directed to only a few of the very many variables which can be used in the practice of the method of the present invention, it should be understood that the present invention is directed to the use of a much broader variety of alkali metal carbonates or bicarbonates as well as conditions shown in the description preceding this example.

What is claimed is:

1. A method for making 2-fluoro-2-deoxy-D-glucose comprising,
 - 5 1) effecting an anion exchange reaction between [^{18}F]fluoride ion and an anion ionically bound to an anionic exchange resin, where the [^{18}F]fluoride ion is employed as an aqueous solution of [^{18}F]fluoride ion and 10 to 60 nmol of an alkali metal carbonate, or bicarbonate salt, per μmol of anionic
10 sites on the resin,
 - (2) effecting the displacement of the [^{18}F]fluoride ion on the anion exchange resin of (1) with the trifluoromethanesulfonyl ester leaving group
15 of an organic solvent solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose,
 - (3) treating with an aqueous hydrogen halide solution, the residue of the effluent of (2), after it has been collected from the anion exchange
20 resin and stripped of organic solvent to effect the hydrolysis of the resulting tetraacetyl 2-fluoro-2-deoxyglucose, and
 - (4) recovering the resulting [^{18}F]2-fluoro-2-deoxyglucose from (3).
2. A method in accordance with claim 1, where the anion on the anion exchange resin is a carbonate or bicarbonate anion.
3. A method in accordance with claim 1, where the anion exchange resin is a polystyrene resin functionalized with piperidinopyridinium groups.
4. A method in accordance with claim 1, where the alkali metal bicarbonate used in combination with [^{18}F]fluoride ion is sodium bicarbonate.
5. A method in accordance with claim 1, where the organic solvent is acetonitrile.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/02366

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : C07H 1/00

US CL : 536/18.4, 18.5, 18.6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/18.4, 18.5, 18.6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	Nucl. Med. Biology, volume 17, No. 3, issued 1990 Steven A. Toorongian et al. "Routine Production of 2-Deoxy-2-[18F] Fluoro-D-glucose by Direct Nucleophilic Exchange on a Quarternary 4-Aminopyridinium Resin," pages 273-279, see page 274, column 1, line 27 through column 2, line 43.	1-3 and 5 ----- 4



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

01 APRIL 1994

Date of mailing of the international search report

MAY 06 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

James O. Wilson

Telephone No. (703) 308-0196

Jill Warden for

Form PCT/ISA/210 (second sheet)(July 1992)*